Pachyonychia Congenita: A Spectrum of KRT6a Mutations in Australian Patients


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Abstract

Background: Pachyonychia congenita (PC) is a rare inherited disorder of keratinization characterised by hypertrophic nail dystrophy, painful palmoplantar blisters, cysts, follicular hyperkeratosis and oral leukokeratosis. It is associated with mutations in five differentiation-specific keratin genes, KRT6A, KRT6B, KRT6C, KRT16, or KRT17.

Objectives: Living with Pachyonychia Congenita can be isolating. The aim of this paper is to document a single patient’s experience within a national context.

Method: We report the case of a 2 year old female with an atypical presentation of PC due to a mutation in KRT6A with severely hypertrophic follicular keratoses, skin fragility, relative sparing of nail hypertrophy on one hand and failure to thrive in early infancy. In collaboration with the International Pachyonychia Congenita Research Registry (IPCRR), a database search was performed using Australian residency and KRT6A mutation as inclusion criteria. The IPCRR database was also searched for a matching KRT6A mutation. Six Australian patients were identified in addition to one patient with an identical mutation residing in the United States. The detailed standardized patient questionnaire data was manually collated and analysed.

Results: Fingernail hypertrophy and oral leukokeratosis were the most common features. There was no recording of asymmetric distribution in any other Australian patient. Trouble nursing as an infant and follicular hyperkeratosis also occurred in the American patient, however they did not have asymmetric distribution and the oral leukokeratosis appeared later in life.

Conclusion: This case has unique features. Sharing information can assist patients navigating life with this condition.

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Pachyonychia congenita (PC) is a rare inherited disorder of keratinization that affects 5,000 to 10,000 people worldwide (1). It is associated with a mutation in one of five keratin genes (KRT6A, KRT6B, KRT6C, KRT16, KRT17), each defined by a constellation of clinical features. Although historically divided into two types, classification is now based on these genetic subtypes. The International Pachyonychia Congenita Research Registry (IPCRR) has identified more than 100 mutations (2). Characteristic manifestations of PC consist of hypertrophic nail dystrophy, painful palmoplantar keratoderma, cysts, follicular hyperkeratosis, and oral leukokeratosis (2). Painful palmoplantar keratoderma is the most debilitating clinical feature (1).

We report the case of a 2-year-old girl with an unusual presentation of PC due to a mutation in KRT6A. The features of this case are compared with those of other Australian cases of PC with KRT6A defects reported to the IPCRR.

**CASE REPORT**

The patient was born to Pakistani parents who were first cousins. She presented at 7 weeks with abnormal fingernails and white spots on her buccal mucosa. She had poor feeding from birth and was not gaining weight (failure to thrive). The parents noticed nail changes at 10 days and the leukokeratotic plaques, initially thought to be secondary to candida infection, at 3 weeks. Her parents and three older sisters were unaffected.

Initial examination identified hypertrophic dystrophy of her fingernails and toenails, markedly more pronounced on the right hand and foot (Figs. 1 and 2). Leukokeratotic plaques were identified on the tongue and right buccal mucosa. The nail hypertrophy was unilateral, with the left hand completely spared and showing only mild dystrophy of the fourth, fifth, and lateral part of the second fingernails. Similarly, the left foot was relatively spared, with mild dystrophy of only the distal part of the third and fourth toenails. This distribution is difficult to appreciate in the clinical photographs available.

Hyperkeratotic papules appeared over her thighs (Fig. 3) and trunk (Fig. 4). Hyperkeratotic papules developed on the knee extensor surfaces when she started crawling at 5 months old and were exacerbated by warm weather. Painful bullae over the soles of her feet developed upon commencement of walking at 12 months. The bullae were noted to have spread over her buttocks and thighs a few months later. This also flared during warm weather and resolved with the change of seasons at 18 months. Leukokeratosis of her mucous membranes fluctuated with time. Angular cheilitis (Staphylococcus aureus–positive culture) was treated with a 5-day course of topical antibiotic (neomycin and gramicidin); subsequent recurrences resolved with shorter 3-day courses of antibiotic.

Treatment of the nails involved tar cream and keratolytics, including 10% to 40% urea cream and

![Figure 1](image-url)

**Figure 1.** Hypertrophic, elongated curved and dystrophic fingernails: (A) right hand, 2 months old; (B) right hand, 18 months old; (C) right hand, 19 months old; (D) left hand, 19 months old. Note the relative sparing of the left hand. No evidence of hypertrophy, only mild dystrophy of fourth and fifth fingernails and lateral part of second fingernail.
3% salicylic acid in aqueous cream, in combination with a mechanical paring device and a diamond-tipped grinder. Aluminium chloride hexahydrate 20% was applied to blistered areas daily for 4 weeks. A short course of betamethasone valerate 0.02% and hydrocortisone 1% was prescribed to relieve the irritated hyperkeratotic regions over the trunk and thighs, but her parents did not start this treatment. Systemic therapy with acitretin was offered, but her parents elected to wait until their daughter was old enough to decide for herself.

Sequencing of the known pachyonychia congenita genes identified a heterozygous missense variant in \textit{KRT6A} (c.520T>A; p.Phe174Ile) (3). This variant was predicted to be pathogenic using in silico analysis (p > 0.99) (4). Other disease-causing missense mutations in this position have previously been reported (p.Phe174Val, p.Phe174Ser, p.Phe174Cys) (5–8). The
IPCRR reports that this variant has been seen in one other individual in the United States (8), as mentioned in a previous review (3).

**METHOD**

The IPCRR collected data using their detailed standardized patient questionnaire. The IPCRR performed the database search using Australian residency and *KRT6A* mutation as inclusion criteria, which revealed seven individuals with the *KRT6A* mutation registered in Australia, including our patient. One of the seven patients was excluded because of incomplete data (multiple unanswered survey questions). The remaining six patients had incomplete data for no more than one survey question. The IPCRR worldwide database was also searched for a matching *KRT6A* mutation, which identified the aforementioned patient residing in the United States who shares the same mutation as the patient described in this case. The questionnaire data were then used to analyze the spectrum of clinical presentations in all known individuals with the *KRT6A* mutation in Australia in addition to the patient with the same mutation from the United States.

![Figure 3](image1.png)

**Figure 3.** (A) Hyperkeratotic papules over the legs that are worse on the right side, at 18 months old. Area of hyperkeratotic papules on the right upper thigh where blisters were previously present: (B) left leg, 18 months old; (C) 19 months old.

![Figure 4](image2.png)

**Figure 4.** Hyperkeratotic papules over the torso, worse right of the midline: (A) 19 months old and (B) 2 years and 2 months old.
RESULTS

The six Australian patients were from four different families and shared four different mutations (8). Table 1 presents the clinical features that these patients reported. Fingernail hypertrophy and oral leukokeratosis were the most common features, recorded by all six patients. In five of the six patients, these changes were documented to have occurred before 1 year of age. Follicular hyperkeratosis occurred in four of the six patients. Hoarseness of voice was reported in half. There was no recording of asymmetric distribution in any of the other Australian patients. Trouble nursing as an infant was reported in one other patient, but data for this survey question were missing for three patients.

Columns 3 and 4 of Table 1 contrast our patient with the patient from the United States. Follicular hyperkeratosis was a shared clinical feature, but the American patient also had pilosebaceous cysts. The American patient did not have asymmetric distribution, and oral leukokeratosis appeared later in life. Both of these patients reported trouble feeding in infancy.

One section of the IPCRR questionnaire focused on factors found to exacerbate and relieve symptoms. The six Australian patients unanimously reported that rest, reduced mobility, cool weather, and winter relieved their symptoms. Half of the patients described their symptoms as at their best in the morning, and two-thirds reported that wearing cotton socks helped to maintain their feet in optimal condition. Factors collectively acknowledged to contribute to deterioration in symptoms included hot weather, walking, and hot or sweaty feet.

DISCUSSION

PC is a rare and complex genetic disorder. The IPCRR shows that, as of October 2014, there were 593 genetically confirmed cases of PC, 13 of these in Australia (2). Inclusive of our patient, 7 of the 13 documented cases in Australia have a mutation in KRT6A, with the remainder consisting of KRT16 and KRT17 mutations (2).

The hallmark features of PC due to a KRT6A mutation include early onset and extensive nail disease, in addition to substantial disease in locations other than the palms and soles, namely oral leukokeratosis, cysts (pilosebaceous and steatocystoma), follicular hyperkeratosis, and hoarseness of voice (8). This is confirmed in the IPCRR data from the six Australians with PC due to a KRT6A mutation (Table 1). The unique aspects of our case include
relative sparing of fingernail hypertrophy on one hand, severe follicular hyperkeratosis, and blistering involving the proximal limbs. In the Australian cohort, there are no other reports of nail hypertrophy relatively sparing one hand, although one patient described skin calluses affecting the right hand only. New dominant mutations may arise post-zygotically, resulting in somatic mosaicism and asymmetric clinical features. This could be investigated by testing a sample of DNA taken from unaffected tissue, but this was not possible in this case. Unaffected tissue might be expected to show no mutation, whereas minimally affected tissue may contain a smaller proportion of cells with the mutation.

Follicular hyperkeratosis occurs in 80% of individuals with PC due to a KRT6A mutation and is typically located in areas susceptible to friction (1). All Australian patients reported follicular hyperkeratosis (Table 1). Worldwide, IPCRR data show that in individuals with a KRT6A mutation, rates of plantar keratoderma exceed those of palmar keratoderma (2). Because blisters tend to arise in areas of keratoderma, they too are more frequently observed in the plantar region. As evident in this case, the presentation of blisters on the proximal limbs is unique, with no preceding accounts in the literature.

Feeding difficulty and failure to thrive have been reported in two other patients, including the U.S. patient. A possible explanation for this is that leukokeratosis is painful, although the data from the US patient do not support this theory, because the feeding difficulty in infancy predates the appearance of leukokeratosis at 10 to 14 years of age (Table 1). We wonder if failure to thrive is an underreported feature of early infancy in individuals with PC.

As reflected in the Australian data, KRT6A is the most frequently mutated gene, followed by KRT16, KRT17, KRT6B, and KRT6C (8). Our case represents one of more than 45% of cases of PC that arise spontaneously in patients with no family history (new mutations) (1). The history of consanguinity proved to be irrelevant in this case, as this was a new mutation (autosomal dominant) rather than a recessive disorder. Because atypical features of PC were present, we considered the possibility of a second disorder related to consanguinity, but there were no other clinical features to suggest a specific second diagnosis. The possibility of modifying factors related to consanguinity cannot be excluded.

REFERENCES